DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL

OPEN SESSION

PMA P870024/S043

Friday, January 18, 2002

8:34 a.m.

Hilton Washington DC North/Gaithersburg
Salons A, B and C
620 Perry Parkway
Gaithersburg, MD

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Michael R. Grimmett, M.D., Voting Member
Alice Y. Matoba, M.D., Voting Member

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Anne L. Coleman, M.D., Ph.D., Consultant, deputized to vote
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. WEISS: I would like to call this meeting of the Ophthalmic Devices Panel to order, and we will have introductory remarks from Sara Thornton.

Introductory Remarks

MS. THORNTON: Good morning, and welcome to the 103rd meeting of the Ophthalmic Devices Panel. Before we proceed with today's agenda, I have a few short announcements.

I'd like to remind everyone to sign in on the sign-out sheets that are out on the registration table. That's just outside the meeting room. You probably walked by it. But please sign in for us, because we appreciate knowing who has attended.

All handouts for today's meeting are available on the registration table for you. Messages for panel members and FDA participants, information or special needs, should be directed through Ms. Ann Marie Williams, who is available in the registration area. The phone number for calls to the meeting area is (301) 977-8900. That phone is at the registration desk.

In consideration of the panel, the sponsor and the agency, we ask that those of you who have cell phones and pagers either turn them off, please, or put them on vibration mode for the duration of the meeting while you're in this room. And we ask that all meeting participants speak clearly into the microphone, give your name, so that the transcriber will have an accurate recording of your comments. We had some problems yesterday, and I would just like to remind everyone to speak close and directly into the microphone.

All available information for the meeting that we have tentatively scheduled for March 14th and 15th will be on the FDA Advisory Committee web site in approximately one week.

Now at this time I would like to extend a special welcome, and introduce again to the public and the panel and the FDA staff, two panel consultants who are with us for the first time at this meeting, and we have a new panel consumer representative as well.

Dr. Richard Casey, to my right, comes to us from Los Angeles, where he is an Associate Professor of Ophthalmology at the Jules Stein Eye Institute and the Interim Chairman of the

Department of Ophthalmology at the Charles Drew University of Medicine and Science. His clinical practice involves the management of corneal and anterior segment disease, cataract and refractive surgery.

Dr. Janine Smith, to my left, is the Deputy Clinical Director at the National Eye Institute of the National Institutes of Health in Bethesda, Maryland. Her basic science research has been immune-based diseases of the ocular surface, with additional responsibilities for the NEI Intramural Clinical Research Program.

And Ms. Glenda Such, again to my left, the consumer representative to the panel, is the Director of the Computer Training Programs in the Department of Career Services at the Lighthouse International in New York. She is a recognized expert in the field of adaptive technology for visual impairments and the functional implications of visual disabilities, particularly low vision.

We very much appreciate your commitment to serve, and we welcome you to the panel table today.

To continue, will the remaining panel members please introduce themselves, beginning with Dr. Harris?

DR. HARRIS: Oldest first. Thank you.

[Laughter.]

MS. THORNTON: I didn't say that.

DR. HARRIS: Sally said that I'm the one with historical perspective because I was on the panel when Franklin came here with bifocals.

[Laughter.]

DR. HARRIS: Not true. I'm Michael Harris. I'm the Associate Dean and Clinical Professor at the University of California School of Optometry, where I am also chief of the Contact Lens Clinic. I'm also an attorney at law and member of the California State Bar.

DR. EDRINGTON: Tim Edrington, Professor at Southern California College of Optometry.

DR. McMAHON: Tim McMahon, Professor and Director of the Contact Lens Service in the Department of Ophthalmology at the University of Illinois/Chicago.

DR. MATOBA: Alice Matoba, Associate Professor of Ophthalmology, Baylor College of Medicine.

DR. BRADLEY: Arthur Bradley, Professor of Vision Science, Indiana University.

DR. WEISS: Jayne Weiss, Professor of

Ophthalmology and Pathology, Kresge Eye Institute, Wayne State University, Detroit.

DR. GRIMMETT: Michael Grimmett, Assistant Professor, University of Miami School of Medicine, and Medical Director of Bascom Palmer Eye Institute of the Palm Beaches.

DR. COLEMAN: Anne Coleman, Associate Professor of Ophthalmology, UCLA/Los Angeles.

DR. HO: Good morning. Allen Ho, Associate Professor of Ophthalmology, Thomas Jefferson University, Wills Eye Hospital.

DR. VAN METER: Woodford Van Meter, Associate Professor of Ophthalmology, University of Kentucky in Lexington, Kentucky.

MR. McCARLEY: Rick McCarley, President of the Voc Tech in Boca Raton, Florida. I'm the industry representative.

DR. ROSENTHAL: Ralph Rosenthal, Division Director of Ophthalmology and ENT, Food and Drug Administration.

MS. THORNTON: I'd like to read now the conflict of interest statement for today's meeting.

The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude

even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interests of the government.

Therefore, a waiver has been granted for Dr. Michael Harris for his interests in a firm that could potentially be affected by the panel's recommendations. The waiver allows this individual to participate fully in today's deliberations. Copies of this waiver may be obtained from the agency's freedom of information office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration matters regarding Drs. Arthur Bradley, Timothy Edrington,

Michael Harris, Allen Ho, and Timothy McMahon, who reported interest in firms at issue but in matters that are not related to today's agenda. The agency has determined, therefore, that they may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you, Dr. Weiss.

DR. WEISS: Thank you, Sally. We now will begin the open--

MS. THORNTON: I had one more thing. Sorry. I do need to do this before we proceed, the appointment to temporary voting status for those who are here at the table.

"Pursuant to the authority granted under the Medical Devices Advisory Committee charter

dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for this meeting on January 18, 2002: Drs. Allen Ho, Timothy McMahon, Anne Coleman, Richard Casey, Janine Smith, Woodford Van Meter, Timothy Edrington, and Michael Harris. In addition, I appoint Dr. Jayne S. Weiss to serve as Acting Panel Chair for the duration of this meeting.

"For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting." Signed, Dr. David Feigal, Director of the Center for Devices and Radiological Health, January 9, 2002.

Thank you, Dr. Weiss.

OPEN PUBLIC HEARING

DR. WEISS: We will now begin the open public hearing for up to a half hour. I would ask that anyone who has any comments to make will identify themselves and any financial or other potential conflicts that they may have.

We have been informed that Dr. Marjorie Rah has a presentation to make during this portion. Dr. Rah?

DR. RAH: Dr. Marjorie Rah. I'm an Assistant Professor at the New England College of Optometry. What I'd like to present this morning is results, preliminary results from an independent study that I have conducted there. I do not have any personal financial interest in the sponsor and I am not an investigator on their PMA. I'd like to thank the panel for giving me the opportunity to speak this morning, and I would like to acknowledge that I do have an unrestricted grant from Paragon Vision Science that was provided to the Ohio State University to in part fund the project.

The purpose of the project, "The Lenses and Overnight Orthokeratology Study," was it's a pilot study designed to evaluate the safety and efficacy of overnight orthokeratology. It's a multi-center pilot study. Data collection was conducted and is ongoing at the Ohio State University College of Optometry, the New England College of Optometry, Southern California College of Optometry, and we have one investigator who has relocated to the Southern College of Optometry in

Memphis, but there is no data collection being conducted there. The study is being conducted under the FDA IDE G990205.

Sixty patients have been fitted in the study, 25 with the Fargo 6 orthokeratology design and HDS material. The remaining 35 were fitted with the Paragon CRT design and HDS material. Patients are being followed for one year, and what I'm presenting today is a collection of the three-month data.

Inclusion criteria included a sphere power of minus 1 to minus 350; cylinder up to 2 diopters at any axis but no more than 3.5 diopters at any meridian. All participants must be at least 18 years of age and not more than 39 years of age at enrollment, and have a visual acuity of at least 20/20 in each eye with manifest refraction. Current RGP wearers were asked to abstain from lens wear for at least two weeks prior to enrollment. Soft lens wearers were not asked to do so.

Our patients were excluded if they showed any sign of corneal disease or other ocular disorders which would affect their vision; if they had undergone previous refractive surgery or previous or current orthokeratology treatment; if

they had any known sensitivities to the contact lens solutions; use of any medications that might alter the corneal curvature. We excluded pregnant and lactating women and anyone who was intolerant to contact lenses.

The examination visit schedule included a baseline examination, which was a comprehensive exam with the contact lens fitting; following that, a dispensing visit; a one-day, one-week, one-month, three-months, six-months, and one-year visit. At the one-day through six-months visits, this included a morning visit which was immediately after awakening; they would get ready, come straight in, we would remove their lenses for them. The second visit was at least six hours later.

The testing that was conducted at each visit included an unaided high and low contrast Bailey-Lovie visual acuity; keratometry; corneal topography; manifest refraction; biomicroscopy; a contact lens comfort and self-rating of vision questionnaire; and the RSVP quality of life questionnaire.

At three months, 31 of 60 patients had completed the three-month visit. Fourteen patients discontinued prior to the one-month visit for

reasons such as poor adaptation, lack of motivation, and treatment failure. Fifteen additional patients discontinued between the one-month and three-month visits for similar reasons. And I might add that we believe that at least a quarter to a third of the attrition may be attributable to a learning curve on the part of the investigators in fitting the lenses.

At baseline, the means spherical equivalent refractive error was just over minus 2 diopters in each eye for the participants, and the mean change that we noted at three months was also just over 2 diopters. This graph shows a trend in the manifest refraction data. You can see from this graph that most of the change occurs between baseline and one month, with about a quarter to a half diopter of change also occurring between one month and three months.

Unaided visual acuity at three months, 74 percent of the right eyes were 20/20, 61 percent of the left eyes were 20/20 or better, and 93 percent of right and left eyes were 20/40 or better.

At one month, 89 percent of the subjects were within plus or minus 1 diopter of the target. Those who were not, all except one were

undercorrected at that point. At three months, 90 percent of the subjects were within plus or minus 1 diopter of target, and again, mostly undercorrected.

Biomicroscopy findings, no patients had corneal infiltrates at any of our visits. Corneal staining was noted in 77.4 percent of the patients at the morning visit, but I must mention that only two of those patients had a grade higher than a two on that staining. By the afternoon visit this had dropped to 37.9 percent, and none were higher than a grade two, and only one case of staining had to be treated.

Imprinting, which does not appear to be an adverse finding, was found in 13.4 percent of the patients at the three-month morning visit. There was no sign of imprinting at the afternoon visit at three months.

Microcysts were found in 38.7 percent of the patients at the morning visit. All were less than 10 in number, and that had reduced to 26.7 percent of the patients by the three-month afternoon visit, again, all less than 10 in number.

Complications that were reported, we have four documented. Two were for the same patient.

One patient had an insect that flew into her eye while she was riding her bicycle. She was not wearing her lenses at the time. However, she felt better by the time she got home. She put the lens back in. It aggravated the eye. Her corrected visual acuity was 20/25 the morning that she came in after that. It was 20/20 by the second morning. She was treated with an antibiotic, and was able to return to the lenses after treatment was complete.

A second patient reported pain in his right eye in the morning after he inadvertently wore his left lens on his right eye. Again, he was treated prophylactically with an antibiotic, and uncorrected visual acuity was 20/20. He also after treatment was able to go back to wearing lenses.

One patient came in for a regular follow-up visit and a foreign body was found in her eye. The patient was unaware of the foreign body. It was removed at that visit. She was treated with an antibiotic, and she was able to return to lens wear after treatment.

No permanent corneal damage was observed in any of these complications. All patients were able to resume lens wear after their treatment.

And in conclusion, I would just like to

say that we have found that orthokeratology can produce an improvement in visual acuity and can reduce myopic refractive error as long as retainer lenses are worn. The changes can be maintained, from our data, for at least six hours after lens removal, and from our sample we have found it to be a safe and efficacious procedure.

Thank you.

DR. WEISS: Thank you, Dr. Rah. I would ask if any members of the panel have any questions for Dr. Rah?

[No response.]

DR. WEISS: Thank you for that presentation. Is there anyone else who would like to make a comment during this open public hearing?

If not, this will close the public hearing session. There are no division updates in the open committee session which we will now start, so we will then go on to the sponsor presentation of PMA P870024/S043, and you can begin.

PMA P870024/S043

SPONSOR PRESENTATION

DR. MEYERS: Good morning, good morning. My name is Bill Meyers. I'm the Vice President of Science and Technology for Paragon Vision Sciences.

Today we are presenting the data on our PMA for contact lens corneal refractive therapy.

I'd like to present the members of the team who will be making that presentation:

Michael DePaolis, Dr. Michael DePaolis, clinical investigator in this study; Dr. Mark Bullimore, who is Associate Professor at Ohio State University; Dr. Oliver Schein, who is a Professor of Ophthalmology at Johns Hopkins University; Dr. Jerry Legerton, who was the clinical monitor for the Paragon Vision Sciences Study; and Dr. John N. Quiring, who was the biostatistician and is President of QST Consultations.

The device for which we are seeking approval is a contact lens for corneal refractive therapy. The purpose of the device is the temporary reduction in myopia by the application of a rigid gas permeable contact lens having on its back surface a greater apical radius than the pretreatment apical radius of the cornea.

The indication is for the temporary reduction of naturally occurring myopia from minus one-half to minus 6 diopter sphere in the presence of cylinder up to 1.75 diopters. This is performed in an overnight fitting program, differing from

extended wear in that in this indication one puts the lenses on before going to bed and removes them shortly after awakening.

We are seeking approval for this device in both paflufocon-B and paflufocon-D. These materials are already approved by FDA for seven-day extended wear. We are submitting labeling for two configurations of the device, the Paragon CRT configuration, which is the one that was used in the study exclusively, and the Quadra RG, a reverse geometry design for which Paragon has already received approval in the daily wear indication.

So, with no further ado, I'd like to introduce Dr. Mark Bullimore for historical considerations for this PMA.

DR. BULLIMORE: Good morning. My name is Mark Bullimore. I'm an Associate Professor at the Ohio State University. I have no direct financial interest in the products being discussed this morning. I am a paid consultant for Paragon Vision Sciences, and I'm also a recovering panel member.

[Laughter.]

I'd like to start with a brief historical review so that we can consider today's PMA in the appropriate scientific perspective. There is a

literature on orthokeratology and the reshaping of the cornea with rigid contact lenses.

Many of you would be familiar with the Polse study, the Berkeley orthokeratology study. Interestingly, this was one of the first randomized clinical trials funded by the National Eye Institute, conducted some 20 years ago, and this involved randomization of patients to daily wear of lenses. Patients were either randomized to a standard fitting lens or an orthokeratology modality where the lens was considerably flatter than the corneal curvature.

Polse and his colleagues found a mean reduction in myopia of around 1 diopter, an improvement around about two and a half lines of visual acuity, and a return to baseline after discontinuation of lens wear. They also established the safety profile for this modality.

Subsequent advancements in lens designs, particularly the introduction of reverse geometry lenses, resulted in the FDA approving two devices for daily use. The data that are on file for these two submissions demonstrate a mean reduction in myopia of around about 1 and three-quarters diopters, and both of these devices are approved

for up to 3 diopters of myopia.

A couple of studies I'd like to mention that elucidate the mechanism underlying these refractive changes. The first, by Swarbrick and her colleagues, examined daily wear of orthokeratology for a one-month period, and they found about a 1 and three-quarter diopter reduction in the myopia of their subjects. Interestingly, this study was the first to establish that the response was explained by a redistribution of corneal tissue; that is, rather than a warping or bowing of the cornea, it was a redistribution of corneal tissue, principally the epithelium, that resulted in these refractive changes.

A second study by Nichols and co-workers corroborated this finding in terms of the mechanism, but this time looking at an overnight wear modality. Patients wearing the lenses for 60 days experienced a mean reduction of almost 2 diopters in myopia and a mean improvement of uncorrected visual acuity of five to six lines on a logMAR chart.

The final study I want to put before you this morning is another study by Polse and his collaborators. This was not a study of corneal

reshaping or orthokeratology. This was a study of extended wear using traditional fitted lenses.

I raise this study for two reasons. One is that it involves 201 subjects fitted to the same FDA-approved extended wear materials that we're going to discuss in this mornings PMA. The subjects were randomized to one or either of these materials and wore the lenses for a 12-month period on a seven-day extended wear basis.

It's important to note as well that only 62 percent of these subjects completed the 12-month trial. This is particularly interesting because the subjects were first adapted to daily wear, then went through a period of adaptation to extended wear, prior to these 201 subjects being randomized for these two materials.

I'd like to now talk about some of the considerations in designing the clinical study before you. As you can see, there was a multitude of evaluations conducted, both pre-treatment and during the post-treatment visits. The three I want to draw your attention to are on the next slide.

These include low-contrast visual acuity. This was done using a standardized protocol, using Bailey-Lovie logMar charts and a bilateral scoring

methodology. The study also employed a standardized manifest refraction technique. And these two techniques are important because they speak to the safety and effectiveness outcomes that were the focus of this PMA. There was also careful control regarding the time of examination after the lenses had been removed in the morning.

Let me tell you the data that you're not going to see today: cycloplegic refraction, topography analysis, and endothelial cell count. We decided not to perform cycloplegic refraction. One of the reasons for doing this was, in terms of data quality, cycloplegic refraction has been shown to be less repeatable than manifest refraction.

Our other reasons for this choice speak to the issue of respondent burden. We didn't want to subject our subjects to periodic cycloplegic refraction when we were dealing with a temporary treatment for myopia, and we felt that the only benefit of conducting cycloplegic refraction would be to find some very rare cases of pseudo myopia or other accommodative anomalies.

Corneal topography was performed throughout the study by these investigators. Topography was used as a screening tool at study

entry, and it was also used for quality assessment of lens centration during the treatment phase of the study. However, we did not subject post-treatment corneal topography to any rigorous statistical analysis.

Our reasons for not doing this are as follows: We had 11 clinical sites with a multitude of different corneal topographers. So in addition to the problems of data reduction with these devices, there was the issue of different machines using different algorithms and different technologies, and really there is no accepted standard for the analysis of these data.

We also did not measure endothelial cell count. I would like to point out, though, that data on endothelial cell count are on record for both of these materials, related to the seven-day extended wear approval by the FDA of both of these materials. I should also like to point out that the average Dk/L, the transmissibility of the lenses used in the current study, is greater than those used in the extended wear methodology. I would also again like to point out that we're talking about overnight wear of lenses here, and not extended wear.

One of the other key issues concerning this PMA is the issue of consistent wear. The patient doesn't get any benefit unless they consistently wear the lens. It's a temporary correction. It involves compliance on the part of the subject throughout the study. They need consistent wear in order to get the efficacy of the device, and you'll see this when we address the effectiveness data later on in this presentation.

I would now like to turn the podium over to Dr. Jerry Legerton to discuss the device.

DR. LEGERTON: I am Dr. Jerry Legerton. I am a paid consultant of Paragon Vision Sciences, and have a financial interest in this product.

I want to help in our understanding here, do a brief description of the device. That's really made up of the design, the materials, and the prescribing system.

As far as the design is concerned, the primary interest in a lens that is fit with an apical radius that's greater than the underlying corneal apical radius is that of proximity control. The other issue that we'll speak to is that of the FDA-approved extended wear materials.

In lenses that are fit with a greater

apical radius than the underlying cornea, as the lens radially--we proceed to the periphery, the lens will then distance itself from the underlying cornea, and a lens design then must have a secondary zone that returns that lens to the proximity of the cornea. It also must have a third zone that is tangent to the cornea in the peripheral area.

The materials involved are the paflufocon-B and paflufocon-D with the ISO/ANSI Dk's of 40 and 100. Again, as Mark has indicated, these have approval for seven days of extended wear.

The prescribing system used by the investigators was one where they had a 65 lens diagnostic system. They calculated the base curve and the power. The base curve was determined to have a radius that the cornea would need to have to have emmetropia or low hyperopia, and that was simply determined by calculation. But in each base curve they had three depths of the return zone, and could then by bracketing determine the depth that would put them in proximity to the cornea. Then there were nine peripheral configurations that were used to find the design that would allow the lens to be tangent to the peripheral cornea, actually

outside of a zone that topography could measure if it were utilized anyway.

In terms of the investigational plan, great effort was made to, as a sort of "first through the gate" here, to make this investigational plan comprehensive. We had 11 geographically distributed sites. We used a double-masked, randomized protocol for the two materials. We submitted the protocol and received the FDA IDE approval for the protocol, the informed consent, and the case report forms, and enrolled the first adult subject and initiated treatment on June 17th of 2000; the first adolescent on April 26, 2001; and the last subject initiated treatment on August 23rd.

You have before you the list of investigators and their locations. For the inclusion criteria, we initially started with age 18 and older, and then that was changed to age 12 and older by approval of the FDA after the three-month interim report was analyzed by staff and approval was given.

The inclusion included patients with between a half and six diopters of myopia with up to 1 and three-quarters diopter astigmatism.

Patients were required to have demonstrated 12 months stability in their refractive status, within a half diopter, and if they were rigid lens wearers, were required to be out of their lenses for four weeks and to demonstrate half diopter keratometry stability on two serial measures. They also had to be willing to return for 12 months of follow-up.

The exclusion criteria follow those that would normally be considered in a refractive surgery procedure or refractive study.

The pretreatment evaluation again was comprehensive, used to screen and determine the inclusion and exclusion criteria, and had particular measurements that would allow us to measure the endpoint, comparing baseline and follow-up measures. Those particularly were the distance on corrected high-contrast logMAR, the manifest refraction, the distance best corrected logMAR, the keratometry, and the psychometric questionnaire.

Hence, the follow-up evaluations have both measures, as well, in your unaided and best-corrected logMARs, your manual keratometry, your applanation tonometry, and to your segment exam and

your psychometric questionnaire.

As far as the examination schedule, beyond the baseline we did conduct examination at dispensing; a one-day visit which was required to be within one hour of awakening. I want to further mention that in the protocol, the patient was instructed to place the lens no more than 30 minutes before retiring, and to remove the lens within 30 minutes of awakening; that no wear beyond that 30-minute time was sanctioned, with the exception of this one one-day visit. So there was no notion that more is better. This was strictly an overnight procedure.

On the two-week, one-, two-, three-, six-, nine-month visits, the patient was to return to the office within three hours of awakening, and hence with no lens in place. The patients were to bring their lenses in case a practitioner wanted to reapply the lens, but no lens was in place at the time of the visit. Subjects were required to have a, we'll call it a wash-out series of examinations at 8, 24, 48, and 72 hours after lens removal in at least one eye.

And this was double-masked and randomized for the two materials. The randomization schedule

provided for intra-investigator randomization that would net an equal number of subjects in the two materials by 10 subjects, and there was an inter-investigator randomization utilizing six different randomization schedules. This was masked from both the investigator and the subject.

In terms of study monitoring, study initiation was conducted to both review the protocol and then to conduct a training in the diagnostic lens evaluation. Through the course of the study there were a minimum of two monitoring site visits, and the utilization of telephone, e-mail and written correspondence to keep a healthy flow of communication between the monitor, clinical monitor, and the investigators.

In terms of the baseline data, we are directing your attention to the demography of the treated and the completed subjects, and we've put them on a single table here for you. You will see that there is a disproportionate number or make-up in gender, more female subjects than male, and if you look to the right, in comparing the treated with the completed, you'll see that shifts a little, where we have a combination of more persistence and more compliance on the part of

female subjects.

In terms of eyes, there were a near-equal number. There were only two subjects that had only unilateral treatment. And in terms of current contact lens history at the time of baseline, you'll see that the make-up has a high composition of prior contact lens wearers. None of the rigid lens wearers were in a former orthokeratology format, nor had any of the subjects in this study previously had any corneal reshaping technology applied.

The age, if you again compare the treated to the completed, the treated includes the adolescent cohort or adolescent arm of the study, with a mean age of just under 34. The completed subjects, as we will speak in the efficacy analysis, are all adult subjects with a mean age of 37.5.

Further, if we look at the make-up of the treated and completed subjects relevant to manifest refraction spherical equivalent, you will see the percentages applied there from zero to 2 diopters, 26 percent, which dropped to 20.2 percent in the completed group. One might speculate a reason, that the need for the treatment may be less in

lower groups. The modal group, we'll say from 2 to 4, increased, and we saw a slight lesser decrease in the 4 to 6 than we saw in the zero to 2 group.

In terms of analysis, we believe it's helpful for you if you can look at the analysis cohort here, and with some understanding of the breakdown and how we met different groups to do different analyses. The baseline evaluation was applied to 218 subjects. Thirteen subjects, most of which lenses were ordered, were not dispensed, or they were not ordered at all.

The net result is that 20 subjects in fact were treated, and we defined "treatment" as at least one night of overnight wear. Of that, we have those that were not due, that 50 subjects that--correct, 50 subjects that were not due for their nine-month exam at the time that the data base was frozen for this analysis. That resulted in 155 on the nine-month, that were due for a nine-month visit. Sixty of those had discontinued, which then gave us the 95 that completed the nine-month visit.

Eleven of those had intermittent wear, and as Mark mentioned, the need for consistent wear, especially prior to the visit, is important to get

an efficacy, we'll say qualified or valid cohort. And so those 11 subjects that either had lost a lens just prior to the nine-month visit or had had intermittent wear were not included in the efficacy analysis, but were included in the safety analysis, and we then net your 84 subjects that were studied for the efficacy analysis.

Discontinuation did occur. Our discontinuation rate is very much similar to the Polse contact lens extended wear study using the same two materials, and you will see that the primary reason for discontinuation is unacceptable vision. In fact--coming back to that, if you would, Tim--of note here, I want to point out, so that we don't raise an inconsistency concern, that this report of 71 subjects discontinuing, I said 60 subjects discontinued, but that was 60 of those that were due for the nine-month. But also we had another 11 that discontinued, that were not yet due for the nine-months.

In terms of accountability, you will see that our accountability for safety exceeds 94 percent at all visits. Most visits it's higher than that. And our accountability for efficacy exceeds 93 percent at all visits, and most visits

again higher than that.

There were lens reorders allowed in the clinical trial, and these lens reorders could be studied in terms of two rationales. One rationale would be that precision is required to get the lenses to perform the way that we desire; that controlling of proximity is important, and centration is absolutely instrumental and essential to get a good result. And hence you will see that poor centration is the predominant reason for lens replacement.

Ten lenses were replaced for loss, damage, or deposit. So in a sense for the completed eyes, 188 completed eyes, we have 60 lenses that were reordered for purpose of either refining the parameters of the lens, improving centration, or because of, the next leading reason would be an undertreatment.

I now introduce Dr. Oliver Schein, who will present to you the safety analysis.

DR. SCHEIN: Good morning. My name is Oliver Schein, and I am here as a paid consultant to Paragon, and in this capacity I have provided input to them regarding the analysis and interpretation of the data from their clinical

trial. I have no proprietary interest in the company or the device.

I'm going to present, probably in the next five to six minutes, data related to the safety on the entire cohort. Following this, Dr. DePaolis will present analogous data on the efficacy from the entire cohort. This is a randomized trial. Dr. Legerton will return following that presentation and show you some comparison data between the two devices that were compared.

Now, there were five safety endpoints that were specified in the original protocol, and first and probably the most important is loss of best spectacle corrected visual acuity. So as not to say that times, that will be BSCVA. The second is a state of having a BSCVA of worse than a 20/40 threshold. Third is serious adverse events, fourth, slit lamp findings, both as traditionally defined in FDA premarket contact lens trials. And the fifth is symptoms and complaints.

So starting with BSCVA, there was no permanent BSCVA loss observed. By permanent we mean persistent through the course of the study. However, there were transient losses that were observed on each visit. For example, at the one-

and two-month visits there were approximately 9 and 7 percent of the population had a BSCVA loss of at least two lines. From three months and subsequently, this leveled off to about 4 percent.

This is termed "transient" because indeed these individuals at subsequent visits were not found to have a BSCVA loss. I interpret this slide myself as indicating that at any random moment in time, at least based on the data available currently, after the initial break-in one might expect about 4 percent of individuals using this technology to have a BSCVA loss of two ore more lines at a particular moment in time.

So these are BSCVA losses, not a BCVA loss, which is a best corrected visual acuity loss. In other words, the acuity could be regained with a contact lens refraction at that same visit. I've already explained why they've been termed transient.

The second outcome there, then, was the BSCVA status worse than 20/40 at each follow-up visit. These are listed for you here. They're largely in the 1 to 2 percent range. None was recorded at the nine-month visit. Again, for each one of these occurrences, they were in a sense

transient, since at subsequent visits they were not measured in the same people.

Adverse events. There were no adverse events that met the criteria for serious or unanticipated. There was one instance of a corneal abrasion upon removing the lens; another case diagnosed as bacterial conjunctivitis; and a moderate case of microcystic edema.

Grade 3 slit lamp findings. The traditional way of presenting these is simply to count the observations of a particular finding across all the visits. It gives you a total number of observations without regard to whether they were all within the same person or not.

Using that kind of crude approach, there were 28 observations overall of Grade 3 or higher. Eighteen of them were of edema. Of note, 17 of these 18 occurred or were reported from one practice, and that practice is at a very high altitude, and that might well be relevant. Ten eyes of six subjects of these 18 observations occurred on the first day, and six of the observations were contributed by one subject over multiple visits.

Nine observations of staining at Grade 3

level occurred in seven eyes of six subjects, and there was one observation of conjunctival injection. Again, no Grade 4 or what are termed severe observations were noted in the study.

Symptoms and complaints. Discomfort was quite prevalent at dispensing. About three-quarters of individuals fit with the lens complained of some degree of discomfort. Now, unfortunately this data or this discomfort data was not in any way scaled. In fact, it's apparent that it's really uncertain as to whether the discomfort was reported even with or without the lenses, but some discomfort was certainly present and prevalent in three-quarters of individuals at dispensing, and down to about 20 percent by nine months.

The only indirect indication that I could find as to the clinical significance of the discomfort was to look at the reasons for dropout. And as you have been shown, the most common reason for dropout was inadequate level of vision. 3.4 percent of the population reported discomfort as the reason for discontinuation.

So to summarize, there were no persistent BSCVA losses or BSCVA worse than 20/40 at nine months, nor were there serious adverse events

observed in this cohort. There were 28 observations of Grade 3 slit lamp findings. They all resolved. None of the Grade 4 was observed. Discomfort is prevalent initially, goes down over time, and doesn't seem to be the principal reason for discontinuation.

Dr. DePaolis will now present the efficacy data.

DR. DePAOLIS: Thank you, Dr. Schein. Thank you, members of the panel. I may draw to your attention the cohort analysis sheet is part of your handout. I know Dr. Legerton discussed it in great detail earlier, but it may also help better understand the different sample sizes at different points during the analyses.

My name is, again, Michael DePaolis, and I am a clinical investigator for Paragon Vision Sciences in the device discussed here within. In that capacity, I am a paid consultant. However, aside from being a clinical investigator, I have no proprietary interest in Paragon Vision Sciences or any of their products.

I'm here to discuss the five primary measurements that we looked at in terms of a device efficacy. They included unaided visual acuity,

with particular attention to the percentage of patients who were able to achieve 20/20 or 20/40 visual acuity. We looked, number two, at reduction in manifest refraction spherical equivalent, or MRSE. We, number three, looked at predictability, with tolerance levels of a half a diopter in 1 diopter. We looked at, number four, stability between two consecutive visits, again with changes of less than a half diopter in 1 diopter refractively. And then we looked at alterations in corneal curvature and absolute corneal astigmatism.

If we looked at uncorrected visual acuity at the nine-month visit--and you'll notice that these are folks who were targeted for emmetropia, and include a smaller cohort for those who were actually able to reach 20/20 acuity predicated on pretreatment 20/20 acuity levels--you'll see that we were able to achieve acuities of 20/20 or better, uncorrected, in 58.4 percent of the population, and in 89.8 percent of the population we were able to achieve uncorrected visual acuities of 20/40 or better. Recognizing that this is just one data point in time, we'll look at the next slide, which will give us unaided visual acuity over time.

I think we glean a couple things from this chart. First and foremost, you can see most of the therapeutic effect was demonstrable within the first month of treatment. And, number two, we can see that over time the percentage of eyes stratified for different refractive errors will actually be similar across the different time points for 20/20 uncorrected visual acuity as well as 20/40 uncorrected visual acuity.

The second barometer we looked at was reduction in manifest refraction spherical equivalent, and I did want to draw to the panel's attention that the efficacy cohort for this determination included patients with a mean refractive sphere of almost 3 diopters of myopia and a mean refractive cylinder of almost an additional half diopter. As you can see, all but one of our eyes at the nine-month data point was able to achieve some reduction in myopia, with the mean reduction for the cohort being 2.59 diopters.

Predictability was the third issue that we wanted to take a look at from an efficacy standpoint, and as this graph depicts, we can see patients' refractive outcomes within plus and minus a half a diopter. This is achieved in terms of

plus or minus a half diopter of target, and achieved within a plus and minus 1 diopter of target.

You can see throughout the various data points there's a slow upward trend from one month to three months, and then things stabilize pretty much beyond the three-month window.

I'm not sure that the discrepancy between plus and minus a half a diopter outcomes and plus and minus 1 diopter outcomes is exclusively related to the efficacy of the device, and may also speak specifically to the limits of agreement in manifest refraction techniques with half diopter tolerances versus one diopter tolerances.

Another way of looking at predictability is a scattergram, where you can see the limits are plus and minus 1 diopter. What I glean from this particular chart is three variables. One is, the device seems to be fairly predictable. Number two, it seems to be fairly predictable over attempted correction ranges from 1 diopter of myopia up to 6 diopters of myopia. And last, but certainly not least, particularly germane for our presbyopic patients, there were no overcorrections of 2 diopters or greater. In fact, we only had one eye

with an overcorrection of a diopter.

Our fourth variable was stability of manifest refraction spherical equivalent between subsequent visits. And when you look at this chart, in one respect you can look all the way over to the right graph which depicts changes between six and nine months that are a diopter or less in manifest refraction spherical equivalent, and argue that that may be a bit liberal. You could also go to the other end of the chart and again, given the limitations of manifest refractions, say that perhaps the half diopter limit is not a good limit to look at either.

I will draw your attention to the middle set of graphs, which is those patients, the percentage of patients that between the six- and nine-month visit had refractive changes, spherical equivalent refractive changes, of less than three-quarter diopters, and demonstrate that stratified across different refractive categories, we had a fairly high percent of patients achieve that outcome.

Another way of looking at refractive stability is the mean of difference between subsequent visits for manifest refraction spherical

equivalent and for average keratometry findings. And, as you can see here, at data points between three and six months and then again at data points between six and nine months, we had fairly good or fairly tight limits.

In fact, if we depict this in the next slide, again you'll see that most of the therapeutic impact occurred within the first month, with a reduction in keratometry and mean refractive spherical equivalent being aptly noted. And then as we go forward from two months through nine months, the mean of difference between visits became sequentially smaller, without evidence of regression, I might add.

The fifth and final variable we looked at was change in corneal curvature. You could see from the previous slide that there was in fact a positive change in corneal curvature, but in the spirit of full disclosure I share this data with you, simply because it's a big enigmatic for me.

If you look at the graph, you'll see that we actually had changes, absolute changes in corneal cylinder, that were fairly inconsistent. The percentage of eyes that had no change, the percentage of eyes that had modest decreases, and

the percentage of eyes that had modest increases clearly do not depict a trend.

Fortunately, I think what we glean from this graph are two things: Number one, the changes in absolute corneal cylinder, be they positive or negative, were relatively modest. And, number two, this may again implicate that our ways of traditionally measuring corneal cylinder in this subset of the population may not be as accurate as we would like it to be.

In light of that last primary outcome, there were two secondary outcomes we elected to look at. One was a reduction in refractive cylinder, and if we look at the next slide, we'll see that the number of eyes that actually had a reduction in refractive cylinder was approximately 50 percent, with a fair number of eyes having no change, and fewer having an increase in refractive cylinder.

The last secondary outcome that we looked at was derived from our psychometric analyses in which we determined patient satisfaction with unaided vision. As you would anticipate with a device of this nature, as we went from pretreatment to six month to nine month, the percentage of

patients who reported good, very good, or excellent unaided vision increased and fortunately remained fairly consistent.

In fact, if we take a look at the nine-month data point, we find the percentage of patients who reported that their unaided vision as a result of corneal refractive therapy was either good, very good, or excellent, far surpassed their pretreatment unaided visual acuity, and was actually fairly comparable with the percentage of patient in the cohort who reported good, very good, or excellent visual acuity with their habitual means of correction going into the study.

So if I were to summarize the efficacy outcomes, particularly at the nine-month visit, this is depicted on the slide and I think it pretty much reiterates what we've just discussed in the past few minutes. We did see a pretty consistent reduction in--improvement, I should say, excuse me--in uncorrected visual acuity. We did see a reduction in both manifest refraction spherical equivalent and flat keratometry. We found the device to be predictable and stable within measurable tolerance levels of a half diopter in both scenarios.

I will at this point turn the podium back over to Dr. Jerry Legerton, who is going to give us the specific analysis of material.

DR. LEGERTON: Jerry Legerton. The analysis by material was conducted using the Rosner statistical method, which recognizes that two eyes within an individual are not independent, but in fact correlated, and makes adjustments in the p-values for that correlation.

We looked at the variables for efficacy of uncorrected visual acuity, predictability and stability, and for safety we looked at the frequency of slit lamp findings or the proportion of slit lamp findings and the symptoms, problems and complaints. For the analysis by material--and if you want to take a pen here and correct your handout, thanks to our trusty statistician, we found that we had made an error in the slide last night by looking at a wrong proportion after the materials were unmasked and switched for some subjects.

But I want to explain how the material masking and unmasking went for some subjects. That of the 408 eyes, 208 by the randomization schedule were put into paflufocon-B, 200 in paflufocon-D.

The protocol allowed the investigator, in the event of concerns in outcome, to contact the monitor and have subjects unmasked. Over the course of the trial, 12 subjects were unmasked.

The reasons for unmasking would be, for example in a case of edema that they believed was due to hypoxia, they could unmask, they could call and have an unmasking, and if it was deemed to be an appropriate step, we agreed that they could do that and they could reorder the lenses. Also, if there were problems of indentation or adherence, they could unmask and they would have the potential to go either direction.

Again, that occurred in the trial in 12 subjects overall, and all of those switched from the paflufocon-B to the -D. Of those that switched, one subject switched back. So the end result, which will be consistent in the report that you were supplied with the slit lamp findings by material, your end will check out that you will have 184 eyes that were only in paflufocon-B--in other words, they didn't involve those that were switched--and there will be 200 that were in paflufocon-D.

At any rate, it was those, it was the non-

switchers that were studied, so we took those that were only primarily in one material. And using the Rosner method to these efficacy variables, uncorrected visual acuity, predictability and stability, there were no statistical significant differences in the efficacy outcome.

The Rosner method was also applied to the slit lamp findings, the symptoms, problems and complaints. And for slit lamp findings there were then 48 statistical tests of hypothesis, that being the different slit lamp measures over all of the visits would give 48 statistical tests, and edema was the only one that approached statistical significance at a 95 percent confidence level, and even that did not support. I'll go back to that.

On symptoms, problems and complaints, there were 72 statistical tests of hypothesis, and halos at the two-month visit was the only one that showed statistical significance at the 95 percent confidence level. Given the number of statistical tests over both materials, over all the findings, this failed to support a hypothesis that there was a difference between materials, or supported the null.

You have before you a summary table of the

nine-month safety and efficacy variable. In the first column it is all eyes, both materials. The second two columns would be the paflufocon-B only and the paflufocon-D only. In other words, those second columns would not include the switchers.

I think what you will appreciate here is that in numerical value, as well as given the lack of statistical significance, but also to appreciate numerical value, that you will see that the results with the two materials--again, one being a high Dk material, one being a super Dk material, are substantially equivalent through both the safety and the efficacy variables.

We thank you for your consideration of our presentation and our submission, and we ask you to consider that these data establish the safety and efficacy of contact lens corneal refractive therapy in paflufocon-B and -D for the overnight treatment of myopia and myopia with astigmatism.

Panel Questions for the Sponser

DR. WEISS: The sponsor can remain at the table, and we are going to proceed to questions from the panel for the sponsor. Dr. Van Meter?

DR. VAN METER: Since there was a substantial dropout because of patients that were

uncomfortable with their lenses or to some degree dissatisfied with their vision, is there anything that you would do differently if you were fitting another 200 patients to rule out some of these patients who you might argue in retrospect probably shouldn't have been fit with the lens anyway? Did you learn anything from the dropouts?

DR. LEGERTON: Yes. More than just life is learning. It was important to us to establish a good diagnostic procedure before we even started, and certainly select qualified investigators, but through the course of the clinical trial we certainly discovered that refinements could be made to the prescribing system. The real importance of establishing that lens centration early on, lenses that don't have adequate depth are going to decenter or tip-tilt and they're going to be more uncomfortable. So I think a lot of it is not so much in the screening of the patient but rather in the diagnostic lens procedure. The next 200 we would do differently in terms of more refinement of the prescribing system.

DR. VAN METER: Well, this is my point. So it's really a fitter's learning curve rather than a wearer's learning curve.

DR. LEGERTON: Could you repeat that?

DR. VAN METER: So you would say it's more of a contact lens fitter's learning curve rather than a contact lens wearer's learning curve?

DR. LEGERTON: Correct. Like a well-fit, well-centering lens improves in comfort. And also the whole issue of unacceptable vision, if you do have lens decentration, much like a decentered ablation, you're going to have an unacceptable visual result. It may not be so much that you didn't result the myopia but that you don't have a centered applanation.

DR. VAN METER: All right. Thank you. This is Van Meter, for the record.

DR. WEISS: Thank you. We're going to have Dr. Grimmett, Dr. Matoba, Dr. McMahon, and then Dr. Harris.

DR. GRIMMETT: Mike Grimmett. First a comment, then a question to Dr. Bullimore. I certainly appreciate the optimistic intimation of hope for us panel members, given your role as a recovering panel member.

[Laughter.]

And now the question. For this indication of overnight orthokeratology, and given the

theoretical benefits of higher Dk materials, I was wondering why would a clinician fit the lower Dk material, the -B type, rather than the higher Dk material, the -D type, for any circumstance. Is there a huge cost difference between them, or some other issue?

DR. BULLIMORE: This is Mark Bullimore. As far as I'm aware of, there are no cost differences between the materials. In addition to the different permeability of the materials, they do have subtle differences in the handling, surface properties. But I would address the question in a couple of ways.

First, I would like to point out that, again, that both of the materials currently are approved for seven-day extended wear. Secondly, we believe our data support that there is no significant difference between the performance of those two materials. And, thirdly, just to reiterate that we are again talking about an overnight wear modality and not extended wear, so one could argue that the permeability of the material is not quite so critical in this modality as it would be in extended wear.

I hope that answers your question.

DR. GRIMMETT: Yes, it does. Mike Grimmett again. I certainly realize that the data did not show a benefit or superiority of one design over the other, and I recognize that. However, as a commonsense approach, as a clinician it would seem to me, if I were the one fitting it, I would want the higher Dk material just because it has theoretical advantages.

DR. BULLIMORE: Mark Bullimore again. Yes, I mean, we would be happy to acknowledge the theoretical advantages, but we really want to give maximum flexibility to the people manufacturing or fitting these lenses to the patient, so that they could go with their own choice. I mean, I don't want to call it a practice of medicine or practice of optometry issue, but it's sort of at that level of preference. I would certainly anticipate that most of our colleagues, given the choice, might go for a higher material, but we're trying to give as broad an opportunity here as possible. So I would acknowledge your concern. Okay?

DR. GRIMMETT: Thank you.

DR. WEISS: Dr. Matoba?

DR. MATOBA: I'm directing this question to the patients who discontinued the study because

of dissatisfaction with their vision. Do you know what the mean refractive error was in these patients? That is, I'm wondering if they were the people with a higher level of myopia, or if there was something to be gleaned from the characteristics of those patients pretreatment.

DR. LEGERTON: The make-up of the subjects that discontinued for unacceptable vision is not skewed for the higher pretreatment refractive errors, and that is very much consistent with the answer that I gave to Dr. Van Meter, that this may be more an issue--unacceptable vision can also be tagged to problems of actually parameter selection within the lens and gaining centration and so forth.

DR. MATOBA: My second question is in regard to the patient satisfaction with vision data. I know that at nine months you said that 91 percent had very good unaided vision. At one month, what percentage of patients would have said the same thing, roughly? I'm wondering how long it takes to reach that level of 90 percent satisfied, good to excellent.

DR. LEGERTON: I have to--that analysis, the analysis has not been conducted yet on the one

month psychometric questionnaire.

DR. MATOBA: Those patients who had suboptimal correction, and maybe not quite good enough to function comfortably, were those people that had just gotten to this state, or what were they told, what to do? What were they told to do, how to deal with that situation?

DR. LEGERTON: Well, first, if one were to speculate on the one month, because of the clustering of discontinuation, where discontinuation occurred, the majority is between dispensing and two months. So if one were still in treatment at one month and filling out a psychometric questionnaire, I think you would speculate that your percentage of good, very good, or excellent is lower and that that is part of the--that would pave the way to an understanding of why someone would discontinue for unacceptable vision.

But the strength of this modality is the capacity to redesign the lens, and we were rather parsimonious about allowing freedom to do all kinds of retreatments in the clinical trial, where in clinical practice that's something that the practitioner might be more free to do, to do more parameter changing and refinement. So I think

there are two sides to that. One is when you intervene to redesign a lens, and how you respond to patient complaints of unacceptable vision.

DR. WEISS: Dr. McMahon?

DR. McMAHON: Tim McMahon. I have a few questions that I hope you can clear up some confusion for me.

You stated this was a randomized mass trial, yet on Tab D, page 265, your opening statement, it says that "This is a prospective multi-center, open label, non-randomized trial." In the very next statement you indicate that it is randomized by material. Can you clarify to me what is--is the only thing that's randomized is the two materials, and everything else is--

DR. LEGERTON: The only thing that was randomized was two materials.

DR. McMAHON: Okay. The second question I have is more of a practical question, and correct me if it's inappropriate. You indicate that the CRT is a trademarked name from the sponsor, from Paragon, yet you also use the term in the procedure, so that CRT corneal refractive therapy and CRT lens are the same thing. Do you propose that the CRT be the name of the procedure for your

product only, or are you going to ask the community to rephrase the term "orthokeratology" to "CRT" for all practitioners

DR. MEYERS: Bill Meyers with Paragon Vision. The name "CRT" is trademarked by Paragon. Corneal refractive therapy is to be available to anyone. We have made an attempt to trademark that name, with the intention that we assure that no one could lock it up. We do not insist that anyone use that name. Anyone who prefers the name "orthokeratology" can certainly do so. We prefer not to.

DR. McMAHON: Thank you. The next question is, thank you for reterming "retreatment" to "reordering" for at least 10 of those patients. There are 70 lenses that were reordered for patients, or 70 patients that had reorders, 60 of which you indicated were for improvements or changes in centration or overcorrection or undercorrection, yet I didn't see any information as to the effect of the change of those lenses. Do you have that data, and can you describe what the effect of these retreatment lenses were?

DR. LEGERTON: There were 60 lenses ordered, reordered for purpose of retreatment,

we'll say, or refinement of prescription, for 188 eyes. We have not conducted a specific analysis as to what the effect of those retreatments were, and I can only speak as, let's say, the monitor and having some processing of the case report forms.

Some patients--well, again, these are for the completed eyes, so it would be fair to conclude that the retreatment was supportive to the fact that the patient survived the clinical trial. But what specifically it did, what it took them from and to, we have not conducted that analysis.

DR. McMAHON: And can you clarify for me when these retreatments occurred? Was it typically the first month?

DR. LEGERTON: The protocol stipulated that retreatments could occur up to that point, and only thereafter with permission from the monitor, from the clinical monitor.

DR. McMAHON: Do you know what percentage of those were after that one-month point?

DR. LEGERTON: I would be speculating, but from again being involved with it, my speculation is probably fairly accurate, that about two-thirds of them were within one month and about another third were thereafter.

DR. McMAHON: Okay. Thank you. And additional question: In the cohort groups that Dr. DePaolis mentioned, there is the group of 125 patients that achieved 20/20 BCVA. Since the entrance criteria for all your patients was basically to have spectacle correction 20/20 VA, does that suggest then there is a number of patients who were unable to see 20/20 with the CRT design? Is that how I should interpret that?

DR. LEGERTON: Yes. That was cited as one of the deviations in the report. The technique used for high contrast logMAR was the Bailey-Lovie letter counting technique, stipulated at a minimal test distance of 14 feet. All but one site was testing at less than 20 feet, most clustering about that 14-foot distance. Since they were recording it in letter count, 50 letters at 14 feet, 45 letters at 14 feet, when then that is calculated to logMAR value, and we allow a logMAR equivalent of 20/20 minus 2.04, when that calculated out to logMAR, there were logMARs that were below .04; could have been .06, .08.

The practitioner believed that their patient had 20/20 because they had done a refraction in an exam chair on a Snelling chart,

and may have had to trial frame that and move to their 14-foot location to do their logMAR test with the illumination control, the proper distance and so forth. So, again, their belief was the patient was a 20/20 patient, but when we statistically--when we enter the database and do a statistical analysis, apply the logMAR calculation, they calculated out at below 20/20.

DR. McMAHON: Last question for right now would be, Dr. DePaolis presented some data that I hadn't seen with regard to decrease in cylinder. Did you guys do vector analysis, which is really in a circumstance like this, since you haven't mentioned anything about what happens to cylinder axis--and Dr. Bradley can actually comment on this much more elegantly than I can--did you guys perform vector analysis on the cylinder changes?

DR. LEGERTON: We did not conduct vector analysis, and that does require clarification. It's the indication, the difference between an indication requesting a claim of treatment of or full correction of astigmatism, and an indication allowing for the inclusion of patients with astigmatism.

DR. McMAHON: You missed me on that one.

DR. LEGERTON: So we are not claiming, we are not claiming and these data don't support that we are correcting astigmatism.

DR. McMAHON: I understand that. That wasn't the point of my question.

DR. BULLIMORE: May I? We did consider--this is Mark Bullimore--we did consider subjecting our data to vector analysis, but we have declined to do that thus far. Really vector analysis, as you mentioned, is a very powerful technique, but its ultimate value is when there is an attempted astigmatic correction, when it allows you to compare, for example in astigmatic PRK, the attempted astigmatic correction and the actual achieved astigmatic correction.

In this PMA, the subtle changes that we observed in refractive astigmatism--and I think we could all agree that they were modest at best--were not an intended outcome. They were in some respects a secondary outcome and a pleasant benefit to the procedure. So we would submit that vector analysis would be of little benefit here because there was no attempt to treat a specific amount of astigmatism in any given patient.

On average, there was only half a diopter

of cylinder in the entire cohort, and I think the change, the reduction that we got would be in the order of a sixth of a diopter of astigmatism. I have to check those numbers. But really it might be of intellectual interest, but in terms of practical benefit here and the indication for the treatment, we thought it was no real benefit.

DR. McMAHON: Thank you.

DR. WEISS: Dr. Harris?

DR. HARRIS: Michael Harris. Several questions having to do with the submittal and the presentation today. In the submittal you're asking for approval of two different designs: the CRT which you presented data on today, and which was submitted to us in the Quadra RG. I have seen nothing to support, nothing on this particular design, and I'm wondering what is the basis for us to consider approving this other design.

DR. MEYERS: Bill Meyers with Paragon. Corneal refractive therapy or orthokeratology requires a contact lens that has three elements. Those elements are a central base curve, typically spherical; a peripheral region which is designed to, in one way or another, align itself to or be tangent to the cornea, in order to maintain

centration; and a connecting zone that connects those two.

The difference between these designs is primarily in that connecting zone. The function of the lens as such is similar between the two. And, as I mentioned earlier, we do have an approval for that design in daily wear. We felt that the issues here were issues of safety, not of efficacy, since the efficacy of that other design had been demonstrated and is well known in the industry.

So we did not include it in the study, and of course including it in the study would have made the study much more difficult, in that there would have been an additional randomization required. This lens is manufactured, this design was manufactured at Paragon under Paragon control, and we could essentially assure that it was identical one to another, and we wanted to avoid that confusion.

DR. HARRIS: As a follow-up--Michael Harris--do you have any data on the Quadra RG material, either as to safety and efficacy, that you would like us to consider, that hasn't been submitted previously?

MS. THORNTON: Michael, could you repeat

that a little louder into the microphone, please?

DR. HARRIS: Yes, ma'am. Thank you.

MS. THORNTON: Thank you.

DR. HARRIS: Do you have any data supporting the safety and efficacy of the Quadra RG material that you would like us to consider, that has not been previously submitted to the panel?

DR. MEYERS: I'm not exactly sure--I'll let Jerry Legerton--do you want to go ahead, Mark?

DR. BULLIMORE: Mark Bullimore. In terms of the safety of the Quadra RG, traditionally--and maybe somebody could correct me here if I misstate this--approval for contact lenses has been based on material and indication. As far as the Quadra RG lens that we're asking you to approve, or the Quadra RG design we're asking you to approve as part of this PMA, the material and the indications are identical. We would submit, in the absence of any data, that the safety profile of the Quadra RG design should be considered equivalent to the safety profile of the CRT design, based on the materials and the general underlying principles of the design.

As far as the efficacy is concerned, we would again submit that the efficacy has already

been demonstrated through the daily wear approval. Now, the panel and the FDA may want to consider subtle differences in the labeling for the two designs, and we would be happy to sort of discuss that further, but I hope that addresses your question.

DR. HARRIS: Thank you. The protocol calls for following 150 patients for nine months, yet only 85 completed the nine-month study. What happened to the other some 65 subjects that you were supposed to be completing?

DR. LEGERTON: Through the course of the clinical trial--Jerry Legerton. Thank you. Through the course of the clinical trial, we had discussions with FDA staff relative to submission of the PMA, and proceeded with the understanding that a submission of at or about 100 subjects completing a nine-month clinical trial would be acceptable to proceed with the PMA. We appreciate that the initial guidance given by the Ophthalmic Device Panel was for that greater number.

DR. HARRIS: Michael Harris again. The data submitted indicates that there were 11 eyes fitted that were outside the eligibility criteria. Were they included in the data analysis?

DR. LEGERTON: The 11 subjects that completed but weren't in the efficacy analysis, is that what you're speaking to?

DR. HARRIS: You indicate, on 105 of the submittal it says that there are 11 eyes that were outside of the eligibility criteria, departures, and I'm wondering if those are included in the data analysis.

DR. LEGERTON: Yes. We have, again, all eyes treated are in the safety analysis, and we have the breakout for the cohorts.

DR. HARRIS: And my last question for this particular time: There is some concern about treating adolescents, patients under 18 who are minors. You have indicated that some were treated and eventually not included. Can you discuss with us how you wish us to evaluate the use of this lens for patients under the age of 18?

DR. BULLIMORE: Mark Bullimore. It was the intention at the commencement of the trial that the population under study reflect the population that the sponsor believed that the lens would be used upon, and in initial discussions with the FDA the sponsor's plan was to include subjects in the trial of age 12 and above. Initially, the FDA

exhibited a preference that the initial cohort not include people below the age of 18, and so the initial cohort of subjects that were recruited were 18 and above.

It was only subsequent to that that the FDA permitted the enrollment of subjects 12 and above, and it's because of that time line we are unable to provide you today with safety and efficacy data on a complete adolescent cohort. Now, the adolescent subjects are included in the safety cohort and the analysis that Dr. Schein presented, but they are, because none of them have reached the nine-month period, none of them are included in the efficacy cohort.

We would hope that the wisdom of the panel and the sound clinical judgment of the members might illuminate some discussion on this issue, both in terms of the inclusion of adolescents in a PMA trial and also, of course, in the labeling indications for use of the product. But that's the history of it, and that's why unfortunately you don't have data to review today.

DR. HARRIS: Thank you.

DR. WEISS: We're going to have Dr. Edrington, followed by Dr. Matoba and Dr. Bradley.

DR. EDRINGTON: Tim Edrington. Relative to the materials, was there any difference in terms of adherence or imprint?

DR. LEGERTON: The incidence of imprinting and adherence was reported only in comment sections and very rarely. There was no statistical analysis on the frequency, but it is in fact very low, and the low incidence was in both materials. We actually speculated early on--even the literature supports that that might be hypoxic-related as well--that it may occur more in a high Dk versus a super Dk material, but in fact it appeared to be near equal in the two. In other words, it occurred in both materials. I can't say near equal. It occurred in both materials, low incidence.

DR. EDRINGTON: Relative to materials again--Tim Edrington--are there any issues in terms of fabrication, with the laboratories making the lenses, when you look at the two materials?

DR. LEGERTON: Jerry Legerton again. Back to the two material issue, and I want to respond--this in part answers a former question.

Again, it is our experience, especially in the rigid gas permeable industry, that a material is approved for an indication and that some

parameter variance is allowed within that. And in fact manufacturing methodologies and the role of one who has the clearance to market that material is to authorize laboratories to manufacture lenses under that approval, and therein have supervision over Good Manufacturing Practices and their methodologies, in essence to say that we must--we take that responsibility to be sure that they have some design control, or they have design control and that they have the process control to produce what they say they produce. That really is our understanding with this, and that is the purpose of the Quadra RG, that that would--it would be under that name, that independent laboratories would be allowed to produce the very lenses they produce today.

We fully appreciate in this particular indication that the precision of the proximity depths, however they achieve them, is a very critical issue, and in applying the approval for the Quadra RG and executing it in the real market, which is where independent laboratories make their lenses, there is a need to also assure that they have the metrology to measure what they say they make. Dr. Edrington, you are right on the mark

there, you know, what the panel want, understanding that the world of rigid gas permeable lenses is primarily a world of independent laboratories manufacturing lenses.

DR. EDRINGTON: Relative to the CRT design, is there a difference--

MS. THORNTON: Dr. Edrington, could you speak into the microphone a little more? It's hard to capture your voice. Sorry.

DR. EDRINGTON: Relative to the independent laboratories fabricating the CRT design, is there any reason they would be reluctant to do it in the HDS, Hunter design, I mean material, as opposed to the HDS? I'm trying to get at why the HDS would be utilized at all

DR. MEYERS: Bill Meyers from Paragon. Laboratories have preferences. Paragon has demonstrated that any laboratory can manufacture either of these materials. However, there are process differences, and laboratories often have limitations in the number of different processes they like to use. So they have their preferences among materials, and I'm confident there would be some laboratories who would prefer one over the other. But that is not because they cannot do it;

it is only because they choose not to for internal reasons.

That's one of the reason that we studied both materials, is because we knew there would be such preference. Many of these laboratories manufacture a daily wear lens today which are used by professionals across the country. There would be no extended wear, or rather overnight wear labeling, if we do not approve this material. And yet those practitioners who may already feel comfortable doing that, may work off-label without the benefit of labeling, and that was I think primarily our reason for including.

DR. EDRINGTON: From Paragon's perspective, then, assuming that there weren't doctor preferences and laboratory preferences, you would pretty much--would you recommend everybody be putting the HDS 100 material in the CRT design?

DR. MEYERS: Not speaking as a clinician, yes.

DR. EDRINGTON: Okay. One additional question. Maybe this has nothing to do with the FDA. Will practitioners be required to be trained and certified in fitting of this device?

DR. LEGERTON: Jerry Legerton.

MS. THORNTON: Dr. Rosenthal?

DR. ROSENTHAL: That does--

DR. EDRINGTON: Is that outside of the--

DR. ROSENTHAL: No, that is not outside. Rosenthal. That is not outside the purview of the FDA. In fact, if the panel feels that it is an appropriate recommendation, we would appreciate the panel's view on that.

DR. LEGERTON: And that was my answer, too.

DR. EDRINGTON: Thank you.

DR. ROSENTHAL: Thank you, Dr. Legerton.

DR. LEGERTON: That would be your purview, if that's something you felt would be required in the marketplace.

DR. EDRINGTON: Is it within our scope, then, to ask what your recommendation would be or what your plans are?

MS. THORNTON: No, not what his recommendation would be.

DR. EDRINGTON: Okay. Your opinion? How can I ask his?z

DR. ROSENTHAL: Well, I think it really should--this is Rosenthal--I really think it should be up to the panel to make that decision, not up to

the sponsor to suggest to the panel what they would like the panel's decision to be.

DR. WEISS: Maybe I could ask the sponsor, how difficult is it for a practitioner to learn how to dispense this lens?

DR. LEGERTON: Jerry Legerton. There definitely is a learning curve in this modality. Technology can support--I think over time the panel will see probably the application or the desire to apply, let's say, corneal topography in a manner that's different than it has been applied. There might be--or the staff may see software that needs to be validated, that would in fact come up with the final parameters.

I'm convinced beyond a doubt that the precision required in determining the final parameters is far greater than the precision required to determine the final parameter of a rigid gas permeable contact lens. I believe that the noise level of the return zone or the proximity control of this lens or any other person's lens doing the same thing is plus or minus 20 microns. So the question is, how do you get within the plus or minus 20 microns?

And fluorescein pattern reading, which has

been the modo dei, let's say, or the useful, the most used technology for gas permeable lenses, may well have a noise level far greater than 20, plus or minus 20 microns. That would be a reason for the reordering at times. It's not, you're not doing a serial fitting where you're needing two or three lenses, taking it in bits and pieces. But rather the reorders would occur--because this was intended to be a single lens treatment--or did occur in 60 out of 188 eyes, or 60 times for 188 eyes, was for the purpose of refining the parameters.

In answer to your question, specifically how long would it take, or I believe there is learning that a practitioner who has even been in practice a good length of time and fit a lot of lenses, there is some learning that needs to take place, and that is both from an academic point of view and from an experiential point of view.

DR. WEISS: Dr. Edrington, are you finished?

Dr. Matoba?

DR. MATOBA: In regard to those patients who had the best--transient loss of the best spectacle corrected visual acuity, and particularly

the subjects that had worse than 20/40, were they symptomatic at the time this was started? Were they complaining of decrease in vision?

DR. LEGERTON: Jerry Legerton. I would have to try to do a correlation between that visual acuity and their symptoms, problems and complaints. It's interested that that's best spectacle corrected visual acuity.

DR. MATOBA: I would expect their uncorrected to be worse.

DR. LEGERTON: Right. Not necessarily.

DR. MATOBA: Okay.

DR. LEGERTON: They may be 20/32 uncorrected, and put on their spectacles and still be 20/32, and they may be gauging their satisfaction with their vision compared to their pretreatment, like "I was 20/200 before and now I'm 20/32."

DR. MATOBA: Well, if they're satisfied, that's fine.

DR. LEGERTON: So they may not be complaining at all.

DR. MATOBA: But if you don't know the answer--

DR. LEGERTON: I don't. I have not done

that correlation.

DR. MATOBA: And so this was transient, so at subsequent visits they no longer had that. Say at six months we have 3 percent, 4 percent of patients having loss of best corrected acuity, that's another 4 percent of patients. So I wonder why someone would be doing well and all of a sudden at six months they develop a loss or decrease of best corrected visual acuity, and also, were there a subset of patients who had recurring episodes, who kept getting every so often, every few months, some--

DR. LEGERTON: Jerry Legerton. Yes, in the clinical report we have given you a line listing of eyes that lost two or more lines of acuity and then categorized it, and by that it is possible to look and see were there repeat eyes. And if I'm not mistaken, there was one subject that had repeat loss on three visits of let's say the eight visits. There were a couple of others that had repeats on two visits.

But in all cases we were able to verify even those that, let's say, had a loss at a nine-month visit, have been seen subsequently, so we have on every patient the knowledge that on a

subsequent visit the loss was not present. But think the answer to your question is yes, there were some subjects that there were repeat measures of loss of acuity.

DR. MATOBA: And the first part of that second question was, why at some--late in the study, six months into the study, when you assume they are at a pretty steady state in terms of the wearing time and the adaptation to contact lenses, would a patient suddenly develop best corrected visual acuity worse than, say, 20/40?

DR. LEGERTON: Jerry Legerton. I don't recall whether this was Dr. Schein or Dr. Bullimore that I'm quoting, but in this modality it's possible to have a "bad hair day," that on a given night--

[Laughter.]

DR. LEGERTON: --that on a given night a lens can decenter or have less centration, less than optimum centration. And so it is possible on a single measure to have someone who would have a loss and then would not have at another time.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: A couple of questions. There was the implication that the primary cause of

dropout was due to unsatisfactory vision quality, uncorrected, and the primary reason for that was a fitting failure on the part of the clinician. Another way to assess failure is not in the dropped out subjects but those who actually continued through the nine months.

And I'm looking at your achieved versus attempted and there is, as we might imagine, a considerable scatter in the data set, and I'm wondering whether the failures to achieve the attempted, would you claim that that was due to a fitting error, because I think the presenter indicated that might be due to errors in just doing refractions. It seems to me there are two quite different explanations for these types of errors, and I wonder if we could have some clarification on that.

DR. BULLIMORE: Mark Bullimore. As is typical in any refractive therapy, you do get some--you don't get that perfect ratio line and everybody falling about that line. In the order of 50 percent of the patients were within half a diopter of attempted correction, and in the order of 90 percent were within 1 diopter of attempted correction. And yes, you're subject to the whims

of variability of manifest refraction.

But even though patients may be undercorrected by say a diopter or so, it's still possible for that patient to be quite happy with that outcome due to the reduced dependence on other modes of refractive correction. I had dinner with a gentleman the other night who was wearing his lenses on an intermittent basis, and he was trying to find that sweet spot in the middle where he had adequate distant vision and, as a nascent presbyope, had adequate near vision. So I'm not proposing that the label include that sort of intermittent wear, but you don't have to have 20/20 vision and emmetropia to be satisfied with this modality.

DR. BRADLEY: I have a couple of follow-up question on that. In the refitting that went on, were these patients refitted because of undercorrection? And were they refit to increase the intended correct?

DR. LEGERTON: Jerry Legerton. There certainly were a percentage of patients that were refit for undertreatment, and the table says undertreatment, and then poor centration also nets undertreatment. I put back up the scattergram

because you were addressing that, as well.

DR. BRADLEY: Yes. Thanks.

DR. LEGERTON: And if we put sort of a mean line through it, where the mean is, again at nine months it was minus let's say approximately a quarter. One notion is that if one can get a 5 diopter correction on a 5 diopter eye, why do we have undertreatments on 2 diopter eyes?

DR. BRADLEY: Exactly the point.

DR. LEGERTON: Two and a half diopter eyes. And we were fairly rigid in our recommendations in the fitting guide to the investigator, and one piece of rigidity was that we suggested that they or recommended that they calculate the base curve at a half diopter greater than what they wanted the end result to be. If one looked at that and said, "Well, gee, if you're always a half under, why don't you just adjust your nomogram here, your algorithm?" And that in fact is a reality, that if you can get a 5 on a 5 or a 450 on a 5, you should be able to get a 450 on a 450.

DR. BRADLEY: So my final--you've actually made my next two points for me, but the impression I had looking at these data was that you could

certainly, the clinician could certainly do better outside of this study protocol, in the sense that the device has been shown to be able to achieve a fairly large refractive error, and with refitting presumably you can tweak the final achieved refractive error. Is that your expectation?

DR. LEGERTON: Jerry Legerton. Yes. Yes. We expect that the real world result will exceed the clinic trial, these data in terms of the presentation.

DR. BRADLEY: Now I have a completely different topic, really a follow-up from Mike Harris's question about seeking approval for the Quadra lens. The argument seemed to be based upon a couple of equivalences: One, that the underlying theory behind this lens' effect was basically the same as the one that was studied in this PMA. And the second argument was that the device, the Quadra already exists for daily wear.

And it seemed to me that the critical comparison for us, then, was for you to convince us that the overnight effects of the study lens are equivalent to the daily wear effects of that same lens, and by implication we could then stretch the argument to say, well, perhaps we expect a similar

equivalence for the Quadra lens, and therefore we can accept Dr. Bullimore's suggestion that these lenses are equivalent.

DR. LEGERTON: Jerry Legerton. Yes, you have summed that up well. We believe that these data support the safety of this material for this indication, and that parameter variance should be allowed in that, similar to other rigid gas permeable applications. However, since we have not tested all reverse geometry designs for their efficacy, we have in our labeling reduced the efficacy that would be in the labeling to what was established on an eight-hour open eye application instead of an eight-hour closed eye application.

DR. BRADLEY: Thank you.

DR. WEISS: I had one question. Then I think we'll continue with a question by Dr. Grimmett, and then we'll take a 15-minute break before going on to the FDA presentation.

You indicated that many of the cases of corneal edema occurred in the practice which was in high altitude, and so that might be associated with the cause of corneal edema. With that in mind, do you have any suggestions to practitioners as far as a different fit or anything they can be doing to

decrease the chance of corneal edema if they're fitting in a high altitude area?

DR. LEGERTON: Jerry Legerton. I want to address that question back to a little bit more elaboration on the two materials themselves, some statements that weren't made. Both materials have seven-day approval for extended wear.

One of the questions by the reviewers had to do with the overall transmission or average thickness of these lenses, and that's the other thing I wanted to address, that these lenses are all huddled about plano. They have near parallel surfaces, and the thickness of the lenses is about .15 over the whole profile of the lens. That's what we use to support the fact that the actual average transmission of these lenses is greater than the same material used for minus 3 myopes and plus 3 hyperopes in extended wear.

Further, I wanted to point out the work of Hill and others in the past, that the equivalent oxygen percentage requirements of humans follow a normal standard distribution, and there are those that have higher requirements and lower requirements. And one of the values we see of having both materials is that they in fact do

complement each other, and while a particular practitioner may have a prescribing philosophy that their comfort zone is, "I'm only going to use the super Dk material," another may prefer the lower Dk for other reasons, but they vary accordingly.

But I would certainly think that, for instance, the doctor at the 7,000-plus altitude--who happened to have been on the Device Panel for 17 years himself, and was involved in scaling, developing the scaling requirements for slit lamp, so I think he called it right--I don't think he would be inclined to use much of the lower Dk material, and would probably recommend to people at high altitude, you know, if we have that one extra compromise, and given these data, pick the high Dk.

DR. WEISS: Just a follow-up of that. Of those, I think there were seven cases that occurred at the high altitude or something along that--

DR. LEGERTON: There were 17 of 18 eyes with Grade 3--

DR. WEISS: Were in the high altitude. Okay, so of those 17, do you know what percentage had the high Dk/A?

DR. LEGERTON: They were both materials.

DR. WEISS: So there was--

DR. LEGERTON: And it's in the line listing. I can get it for you later and answer, but it's in the line listing in your report.

DR. WEISS: Well, if you suggest that you use a higher Dk if you're in a high altitude area, and let's say half the patients who developed the problem had high Dk, then it has no significance.

DR. LEGERTON: If I may speculate quickly, and maybe one of my colleagues is tabulating, but I would say it was probably--

DR. WEISS: Dr. Bullimore.

DR. LEGERTON: Mark Bullimore can answer.

[Laughter.]

DR. BULLIMORE: Mark Bullimore. Again referring to Attachment 5 on page 76 of the submission to the FDA, I believe I'm right in saying that those 17 cases occurred in 8 patients.

DR. WEISS: Okay, so I said seven.

DR. BULLIMORE: Of those eight patients, so these were the 17 instances or presentations of edema at that high-altitude practice, there were eight patients, of which three were fit with the high Dk material and five with the low, so--

DR. WEISS: Okay, so we don't know.

DR. HARRIS: What page are we looking at?

DR. BULLIMORE: Page 76 in my copy.

DR. HARRIS: Which tab?

DR. BULLIMORE: I'm not working from the same that you are. It's Attachment 5.

DR. HARRIS: Which tab?

DR. BULLIMORE: It's Tab 6 in mine, but that may not be relevant to yours.

DR. LEGERTON: Mike, it's Jerry Legerton. It's Attachment 5 in the Clinical Report.

DR. WEISS: So essentially what we're saying, or what I understand you to say, is we don't really know. You would suggest five patients had the lower Dk but three patients had the high Dk, so they wouldn't have been--we wouldn't be able to offer them any suggestions to decrease the chance of getting corneal edema. So perhaps that will be a labeling issue, just to inform clinicians.

Dr. Grimmett next. Oh, Dr. Edrington.

DR. EDRINGTON: Tim Edrington. Just a follow-up on that. Were those patients discontinued at that time in that practice, or did the edema go away at follow-up visits, when they saw the patient down the road? Were they all at the first visit, or--

DR. LEGERTON: The majority of the reports were day one, and in the majority of the cases the practitioner did not intervene, and in the majority of the cases the edema resolved.

DR. WEISS: Dr. McMahon, was it on this question or something else?

DR. McMAHON: Related.

DR. WEISS: Related? Fine.

DR. McMAHON: I was the reviewer that asked for the transmissibility data, and I still haven't heard. Even though the lenses themselves are in form now of being equivalently plano, I haven't heard what the transmissibility--not permeability, transmissibility--of these two different designs are, of the materials.

DR. LEGERTON: Of the two different designs?

DR. McMAHON: Two materials. Materials. Do you have that?

DR. LEGERTON: To get transmissibility you would need the average thickness profile of both designs. You want to know Dk/L?

DR. McMAHON: Right. I asked that several weeks ago.

DR. LEGERTON: The two materials, yes.

Dk/L of paflufocon-B in the Paragon CRT design is 40. That's a 60 Dk divided by .15. The transmissibility of the paflufocon-D is 100, a Dk of 150, thickness .15.

DR. McMAHON: Thank you.

DR. WEISS: Dr. Grimmett, and then we will take a 15-minute break.

DR. GRIMMETT: Mike Grimmett. I was pleased to see in the open public hearing that Dr. Rah noted she used the RSVP survey, and I'd like to just acknowledge the superlative work that Dr. Schein has done in done in this area in his development of that instrument. I have a question. Was the RSVP survey used in this PMA, or any quality of life survey of that nature?

No. Dr. Bullimore is shaking his head no. Thank you.

DR. WEISS: I want to thank the sponsor for a very clear presentation, and we will reconvene in 15 minutes.

[Recess.]

FDA PRESENTATION

DR. WEISS: We are now going to begin with the FDA presentation, and Dr. Saviola will begin.

DR. SAVIOLA: Thank you, Dr. Weiss. I'm

Jim Saviola. I'm the branch chief of the Vitreoretinal and Extraocular Devices Branch, and I'm going to introduce our review team in just a moment, but first I have some brief general introductory remarks about the topic of orthokeratology and also some specific remarks about this application.

Back on February 12, 1998, the topic of RGP lenses for overnight orthokeratology was the subject of discussion for guidance purposes at an advisory panel meeting held at the Parklawn Building. We also discussed 30-day extended wear lenses for guidance at that meeting, as well.

As membership of the panel changes, most of the advisory members who participated at that meeting have rotated off the panel, with the exception of Dr. Harris.

[Laughter.]

He will serve as a historical reference today, since he was in attendance. Dr. Bullimore was also present that day, but as you can see, he has crossed over to the other side.

[Laughter.]

The other side of the table, that is.

Later that year, on September 25, 1998,

FDA issued a public health notification regarding illegal promotion of contact lenses that addressed both orthokeratology and tinted lenses, and that advisory contained the following statement:

"FDA is not aware of any well-controlled clinical studies published in the literature on the overnight use of orthokeratology lenses. The overnight use of lenses is not considered daily wear, and is considered extended wear, since the lens is worn while the user is asleep."

Since that time, publications have begun to appear in the literature on the topic of overnight ortho-k. However, the study reported before you today represents the most comprehensive effort undertaken and completed to date on this topic. I would like to commend the sponsor for the quality of the submission, not just from the standpoint of making the panel's job and our job at FDA easier, but for advancing the scientific knowledge base on this topic by way of their clinical study.

We have referred this application to you today for your review and recommendations, since this is the first application that we have received that is suitable for panel review for this proposed

indication. Current FDA guidance for industry on submission of ortho-k RGP lenses was issued back on April 10th of 2000. That document recommends a study of 150 to 200 completed subjects, followed for 12 months, for an overnight orthokeratology study.

We brought this PMA to the advisory panel today with nine-month follow-up data because of the sponsor's ability to demonstrate stability of the intended effect at an early time point of the investigation. In your panel pack under the protocol Section 4.5.2, the original protocol did stipulate that it was a nine-month study and they were targeting 150 to 200 subjects to be completed. Excuse me. They were targeting 150 subjects complete at nine months with an enrollment of 200, so they anticipated a discontinuation rate of 25 percent, and as you can see from the data, that was overly optimistic.

However, in the back of your panel packs, the Berkeley study that the sponsor made reference to earlier in their presentation does reflect a certain consistency with the outcome achieved in this study, from the standpoint of successfully completed patients. It seems from current

literature, as well as in this PMA dated today, that the discontinuation rate is going to be much higher than 25 percent.

We do not expect everybody who enters into this therapy to be successful. We do expect limitations with this procedure, and indeed over 50 of the 72 pages of our orthokeratology guidance comprise sample labeling, to inform those candidates and practitioners of the clinical outcomes, to give them some idea of what the expectations might be.

I would like to make an important point for the public to consider. I would like to caution those observers who leave this meeting today with the idea that the panel recommendation applies to all lenses and all RGP materials, from a regulatory standpoint, FDA is considering overnight orthokeratology for the materials and the lens designs contained in this application only. I would like to emphasize the point for the professional community and the public, that today's outcome is not a blanket general recommendation for all orthokeratology designs and all RGP materials.

I would like to thank the FDA review team, both the primary panel reviewers and the internal

reviewers. I would now like to introduce Ms. Eleanor McGhee, the lead reviewer for this application.

MS. McGHEE: Good morning. As Dr. Saviola said, my name is Eleanor McGhee, and I am the team leader for this application. I would like to take the opportunity to introduce the team members, those individuals who played a role in getting this application to the panel:

Dr. Edrington, Dr. McMahon, served as primary reviewers for the application. Dr. Bernard Lepri conducted an in-house clinical review. Dr. Jean Hilmantle for statistical review. Dr. Jimmy Chin for chemistry and manufacturing. Mr. Lev Keely for panel coordination. Ms. Laura Mendelsohn for patient labeling review. Sally Thornton, executive secretary of the panel, for helping us with our coordinating. And Jim Saviola, our branch chief. To all of you, I thank you very much for your timely responses.

I'd like to now turn it over to Bernard Lepri for clinical review.

DR. LEPRI: Good morning, panel members, sponsors, FDA members, and other guests. This morning I am going to present to you a very brief

presentation of some clarification information and the questions, which should all be completed within under 15 minutes, and you'll notice that I'm sitting this one out today because I'm suffering from PTPD, post traumatic PMA disorder.

[Laughter.]

So I now present to you PMA P870024, Supplement 43, Paragon Vision Sciences, Contact Lens Corneal Refraction Therapy. The sponsor is presenting two materials and two designs. They are rigid gas permeable contact lenses for overnight contact lens corneal refractive therapy of myopia with or without astigmatism.

You know who I am. This is a refresher of some of the materials, of the nature of the materials presented to you today. I'd like to remind the panel that both the materials are approved in this PMA, have been approved for seven-day extended overnight wear. The Quadra RG trademark design in both materials has previously been cleared by FDA for daily wear orthokeratology/corneal refractive therapy, not conventional daily wear of RGP.

As some further background information for question number one, the CRT design was the only

one studied overnight with both materials in this PMA, and the primary safety and effectiveness endpoints were all met.

Question number one: Do the data reported for the two different generic lens materials evaluated during this study raise any questions of safety and effectiveness?

Background information for question number two. Both materials were evaluated in overnight clinical trials, and approved. Only one of the designs was evaluated in the trials reported in this PMA. Efficacy of the Quadra RG design is based on prior FDA daily wear clearance for orthokeratology/corneal refractive therapy.

Also, I want to direct the panel's attention to the draft labeling in this PMA, where you would find the outcome results from the prior clearance and review of FDA for the Quadra RG design, so those data are available in the draft labeling in the PMA.

Question number two: Do the data reported for the CRT reverse geometry lens design evaluated during the study raise any questions of safety and effectiveness?

Question number three: Is the length of

follow-up sufficient to demonstrate the stability of the intended myopic reduction with the prescribed maintenance regimen?

Question number four: What are the panel's recommendations for the proposed product labeling, for example, warnings, precautions, terminology to describe the procedure, etcetera?

Question number five: Does the panel see any issues that suggest a need for a post-approval follow-up of the study subjects or a post-approval study?

And question number six: Do the data presented in this PMA provide reasonable assurance of safety and effectiveness for the proposed indications?

Thank you.

DR. WEISS: Dr. Saviola?

DR. SAVIOLA: Before we retreat from the table, I just want to make sure that you folks don't have any questions regarding this issue of the two designs that we might need to clarify for you before you enter in your discussion.

DR. WEISS: Yes, we will entertain those questions or any other questions the panel has for FDA at this time.

There are no questions for FDA? Well, in the spirit of moving ahead, it seems that because this is such a well put together proposal by the sponsor, we are just going to forge ahead with additional comments for the sponsor. And I have had some interest, and I have accepted the interest on the panel's behalf, of skipping lunch and then moving ahead with the committee's deliberation, because it seems that this is going ahead at a good clip.

So are there any additional comments from the sponsor at this point?

There appear to be no additional comments of the sponsor. Lunch being so skipped, we will then proceed with committee deliberations and have the reviews of the primary panel reviewers, first beginning with Dr. Timothy McMahon.

COMMITTEE DELIBERATIONS

DR. McMAHON: Thank you. While we are getting set up, let me preface my comments by acknowledging my appreciation of the sponsor for two things: one, his putting together a superior proposal, certainly relative to what we experienced yesterday. And the second is for being the first out of the gate to deal with this aspect of

overnight orthokeratology in a meaningful and scientific manner, and taking overnight corneal reformation for refractive error from the cult arena to the arena of science.

So this pertains to the PMA as described, and I will limit my comments to issues and questions that are raised in my review, and actually won't go over any overall detail, but specific issues.

As has been previously mentioned, there really is no data provided with regard to the Quadra design, so it really makes it difficult for the panel to make any or certainly for me to make any comments specific to that. At the same time, it is probably reasonably similar. Certainly the materials employed have been previously approved for overnight wear, and the designs have in large context reasonable similarities. However, there is no data.

The issue with regard to transmissibility has been provided just recently. I think a table in the labeling would be useful, particularly so that investigators know whether they're dealing with lenses that adhere to the Holden, Mertz criteria or not. The HDS-100 does. The HDS does